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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/791,618 | 03/02/2004 | Sherman Fong | P1192-2C1 | 4005 |

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| EXAMINER | |
|---|---|
| DEBERRY, REGINA M | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1647 | |

DATE MAILED: 01/27/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/791,618 | FONG ET AL. | |
| | Examiner | Art Unit | |
| | Regina M. DeBerry | 1647 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *27 December 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *11-18* is/are pending in the application.

4a) Of the above claim(s) *11 and 15-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *12-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

### *Status of Application, Amendments and/or Claims*

The amendment filed 27 December 2005 has been entered in full.

The Fong Declaration under 37 CFR 1.132 filed 28 October 2005 has been entered. Claims 11 and 15-18 are withdrawn. Claims 12-14 are under examination.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

### *Information Disclosure Statement*

The information disclosure statement(s) (IDS) filed 27 December 2005 was received and complies with the provisions of 37 CFR §§1.97 and 1.98. It has been placed in the application file and the information referred to therein has been considered as to the merits.

### *Withdrawn Objections And/Or Rejections*

The objection to the specification, as set forth at pages 3-4 of the previous Office Action (29 July 2005) is *withdrawn* in view of the amendment (27 December 2005).

**Claim Rejections - 35 USC § 101**

Claims 12-14 remain rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility for the isolated polypeptide. The instant claims are drawn to

methods of enhancing the infiltration of immune cells in a mammal, comprising administering to said mammal an effective amount of Bolekine polypeptide (SEQ ID NO:2) and a method of alleviating infection in a mammal comprising administering an effective amount of Bolekine polypeptide (SEQ ID NO:2). The basis for this rejection is set forth at pages 4-8 of the previous Office Action (27 July 2005).

Applicant cites the Utility Examination Guidelines and various case law. Applicant argues that Kahan *et al.* (Curr. Opin. Immuno., reference cited by the Examiner), does not review the MLR itself, and that the assay is placed together with all immune *in vitro* assays in his conclusion that, "no *in vitro* immunoassay" is useful. Applicant contends that such a broad generalization is not a compelling reason to reject the Applicant's use of the MLR to provide utility. Applicant states that they have provided a representative number of patents that have been allowed under the new utility guidelines and have used the MLR in support of utility of their inventions. Applicant cites Rashid *et al.* as evidence that MLR, as an *in vitro* assay, can be linked to an *in vivo* result. Applicant argues that the specification discloses that Bolekine has the primary sequence structure of a chemokine and has chemokine activity *in vivo* and *in vitro* assays, which test immune cell proliferation and function. Applicant argues that the specification teaches that Bolekine can be used to limit tumor growth or to activate immune cells in treating infection (instant specification, page 70). Applicant argues that in later published literature, Bolekine (CXCL14 or BRAK), is a cell chemoattractant and has an anti-tumor effect. Applicant cites Shurin *et al.,* Fredrick *et al.,* Schwarze *et al.,* Shellenberger *et al.,* and Sleeman *et al.* as evidence of support (references submitted by Applicant).

Applicant's arguments have been fully considered but are not found persuasive. Firstly, the current rejection is in compliance with the most currently published version of the Utility Guidelines, which require that all biological inventions must have a credible, specific and substantial utility. Additionally, each Patent Application is examined on its own merits. What was deemed allowable in one Patent has no bearing on this application. Rashid *et al.* not only employed the MLR assay, but also examined mitogenic and antigenic stimulation of splenic T cells and the *in vivo* immune response of tumor bearing mice. The instant specification fails to do this. Furthermore, the claimed Bolekine protein tested positive in the MLR assay. The protein of Rashid *et al.* tested negative. Therefore, the results are not comparable. The other literature cited by Applicant teaches that CXCL14 (BRAK) is chemotactic for dendritic cells and has anti-angiogenesis and anti-tumor activities. Applicant has not provided a sequence alignment, which demonstrates that the instant Bolekine polypeptide (SEQ ID NO:2) is CXCL14 (BRAK). Additionally, the instant claims *are not* drawn to methods of inhibiting angiogenesis or treating tumor growth.

Applicant states that in support of the MLR assay and the Vascular Permeability Assay, a declaration under 37 CFR 1.132 from Dr. Sherman Fong has been submitted. In the declaration, Dr. Fong states that Assay # 64 is known as the Miles assay and is well known in the art as an assay to identify proinflammatory molecules. Declarant states that proinflammatory molecules can directly or indirectly cause vascular permeability by causing immune cells to exit from the blood stream and move to the site of injury or infection. Declarant states that these proinflammatory molecules recruit cells

like leukocytes, which includes monocytes, macrophages, basophils, and eosinophils. Declarant states that these cells secrete a range of cytokines that further recruit and activate other inflammatory cells to the site of injury or infection. Declarant states that these processes are critical and tightly regulated via diapedesis and extravasation steps. Declarant concludes that proinflammatory molecules are useful in treating infections, as local administration of the proinflammatory polypeptide would stimulate immune cells already present at the site of infection and induce more immune cells to migrate to the site, thus removing infection at a faster rate. Declarant points to MIP-1 and MIP-2 as being useful to cause neutrophils to extravasate, other CXC chemokines as being useful to activate neutrophils, and other CXC chemokines as being useful to cause chemotaxis of T lymphocytes. Declarant states that inhibitors of proinflammatory molecules are useful to treat diseases characterized by abnormal immune cell response. Declarant states that proinflammatory molecules with angiostatic properties are useful in treating tumors. Declarant states that the Miles assay was initially developed when researching the effect of histamine on the vascular system. Declarant states that subsequent workers have developed the assay into a quantitative one.

This has been fully considered but is not found to be sufficient to overcome the rejection. The Miles assay is useful as a preliminary screen for potential proinflammatory molecules. Basic irritants, such as lye, would test positive in the Miles assay. Further work must be done subsequent to a positive result in a Miles assay to determine if and how a molecule may be useful as a proinflammatory. For example, MIP-1 and MIP-2 are not only positive in the Miles assay, they were also shown to have

the specific activity of causing the extravasation of neutrophils. As Declarant points out, other CXC cytokines, while scoring positive in a Miles assay, have subsequently been shown to have specific activities of activating neutrophils or being chemotactic for T lymphocytes. As was discussed in the previous Office Action, the state of the art shows that a positive result in the Miles assay is insufficient for the skilled artisan to conclude that a molecule is a proinflammatory molecule with specific activities, as opposed to a basic irritant. While particular irritants may have uses that stem from that irritant capability, in the absence of further characterization of what type of reaction the substance causes and what the systemic effects of such are, the result remains a preliminary one, necessitating substantial further research to determine how to use the compound.

Declarant states that the skin vascular permeability assay was used to determine if blood coagulation factor XIII (FXIII) could be used in treating Shonlein Henoch Purpura (SHP). Declarant refers to Hirahara *et al.* (1993, Thrombosis Res. 71:139-148) as showing that FXIII stabilized microvasculature, leading to less permeability, and therefore may be useful in treatment of SHP. This has been fully considered but is not found to be sufficient to overcome the rejection. In the instant case, the claimed Bolekine protein tested positive in the assay. FXIII tested negative. Therefore, the results are not comparable.

Declarant states that the Miles assay was used by Senger *et al.* (1983, Science 219:983-985) to show that a secreted factor called VPF caused vascular permeability. This has been fully considered but is not found to be sufficient to overcome the

rejection. Senger *et al.* set out to determine why vessels lining the peritoneal cavities of rodents with ascites tumors display markedly greater permeability than vessels in control animals. Senger *et al.* only conclude that secretion of permeability-increasing activity appears to be a common feature of tumor cells and that VPR has permeability-increasing activity. Senger *et al.* do not suggest that VPR can be considered a pro-inflammatory molecule useful for treatment of injury or infection.

Declarant states that Yeo *et al.* (1992, Clin. Chem. 38:71-75) confirmed the viability of the skin vascular permeability assay by correlating it with disassociation enhanced lanthanide fluoroimmunoassay (DELFIA) results. Declarant states that VPF (VEGF) tested positive in the skin vascular permeability assay and then anti-VPF antibodies were used to quantify the amount of VPF in the DELFIA. Declarant states that the DELFIA assay has greater sensitivity. This has been fully considered but is not found to be sufficient to overcome the rejection. Yeo *et al.* do not assert that the DELFIA assay or the Miles assay can be used to identify proinflammatory molecules that can be used to treat injury or infection. Yeo *et al.* disclose that VPF may be the same protein as VEGF, which has been shown to be a mitogen specific for endothelial cells, and may promote tumor angiogenesis via its mitogenic activity for endothelial cells. However, the specific and useful activity of VEGF as an angiogenic factor was not identified by the Miles assay or the DELFIA assay. Significant further research had to be conducted to identify this specific and substantial activity.

Declarant reviews the skin vascular permeability assay and refers to Exhibit I as showing a positive reaction for a PRO polypeptide. This has been fully considered but

is not found to be sufficient to overcome the rejection. It is not clear that the PRO polypeptide shown in the exhibit is the same PRO (Bolekine) polypeptide of the instant claims. Furthermore, the assay does not provide the skilled artisan with the guidance necessary for the skilled artisan to determine how to use the claimed PRO polypeptide without resorting to undue experimentation.

Declarant provides his expert opinion that the PRO polypeptide that shows activity in the skin permeability assay has specific, substantial and credible utilities. Declarant states that the application discloses that the results of the skin permeability assay were further analyzed by histopathological examination to rule out inflammation due to endothelial cell damage or mast cell degranulation. Declarant concludes that the vascular permeability observed was not due to histamine release or endothelial cell damage. Declarant asserts that the PRO polypeptides testing positive in the assay are useful to enhance immune cell recruitment to sites of injury or infection, or inhibitors to treat autoimmune diseases. Declarant further states that angiogenic or angiostatic properties of proinflammatory would find utility in controlling tumorgenesis. This has been fully considered but is not found to be sufficient to overcome the rejection. The specification describes analysis of the results of the skin vascular permeability assay as follows:

> The skins are then prepared for histopathologic evaluation. Each site is evaluated for inflammatory cell infiltration into the skin. Sites with visible inflammatory cell inflammation are scored as positive. Inflammatory cells may be neutrophilic, eosinophilic, monocytic or

> lymphocytic. At least a minimal perivascular infiltrate at the injection site is scored as positive, no infiltrate at the site of injection is scored as negative.

As this quotation shows, the Declarant is not entirely correct with respect to the facts. The PRO polypeptides used in the assay are not further analyzed by histopathological examination **to rule out inflammation due to endothelial cell damage or mast cell degranulation**. In this specific case, the Bolekine polypeptide was found to be an irritant to guinea pigs. Such *might* indicate that Bolekine is an inflammatory cytokine (although based on such a result, the person of ordinary skill in the art would not consider that to be a supportable conclusion), or alternatively it might indicate that the guinea pigs are allergic to Bolekine, e.g. that the Bolekine protein has an epitope that the guinea pigs were pre-sensitized to. In either case, the observation is merely a jumping-off point, that is, an invitation to experiment further to determine the properties of Bolekine. Accordingly, the only inflammation that could be treated using anti-Bolekine agents at the time the invention was made is that actually caused by Bolekine, which is a circular exercise with no meaning (as there is no reason to believe that any patient has any condition resulting from excess Bolekine based upon the results in the specification as originally filed). It remains that the skin vascular permeability assay does not give sufficient information so as to inform one of skill in the art as to how to use the claimed polypeptide. The scientific reasoning and evidence as a whole indicates that the rejection should be maintained.

**Claim Rejections - 35 USC § 112, First Paragraph, Enablement**

Claims 12-14 remain rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention. The basis for this rejection is set forth at pages 4-8 of the previous Office Action (27 July 2005).

Applicant incorporates their response to the rejection under 35 USC 101 in response to the rejection under 35 USC 112, first paragraph. Applicants arguments have been fully considered but are not found to be persuasive for reasons of record and the reasons discussed above in the maintained rejection in 35 USC 101. The scientific reasoning and evidence as a whole indicates that the rejection should be maintained.

***Conclusion***

No claims are allowed.

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action.

In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Regina M. DeBerry whose telephone number is (571) 272-0882. The examiner can normally be reached on 9:00 a.m.-6:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda G. Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

RMD
1/24/06

Marianne P. Allen

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PRIMARY EXAMINER
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1/25/06